CLAIMS

What is claimed is:

1. A composition comprising a monoclonal antibody which is capable of binding specifically with a PF4/heparin complex, wherein said antibody preferentially binds with said PF4/heparin complex relative to the binding of said antibody with either PF4 or heparin alone.

2. The composition of claim 1, wherein said monoclonal antibody is capable of binding specifically with a glycosaminoglycan which is not heparin.

3. The composition of claim 1, wherein said monoclonal antibody is capable of activating platelets in the presence of PF4 and heparin.

4. The composition of claim 1, wherein said antibody comprises a heavy chain polypeptide having an amino acid sequence which shares at least about 80% homology with SEQ ID NO:1 and a light chain polypeptide having an amino acid sequence which shares at least about 80% homology with SEQ ID NO:2.

5. The composition of claim 1, wherein said antibody is a murine monoclonal antibody (KKO) which comprises the heavy chain polypeptide of SEQ ID NO:1 and the light chain polypeptide of SEQ ID NO:2.

6. The composition of claim 1, wherein said antibody is a humanized antibody.

7. A composition comprising an isolated nucleic acid, wherein said isolated nucleic acid encodes an antibody which is capable of binding specifically with a PF4/heparin complex, wherein said antibody preferentially binds with said PF4/heparin complex relative to the binding of said antibody with either PF4 or heparin alone, said isolated nucleic acid comprising a nucleotide sequence which shares at least about 80% homology with SEQ ID NO:3 and a nucleotide sequence which shares at least about 80% homology with SEQ ID NO:4.

8. The composition of claim 7, wherein said isolated nucleic acid comprises the nucleotide sequences of SEQ ID NO:3 and SEQ ID NO:4.

9. The composition of claim 7, wherein said isolated nucleic acid encodes a humanized monoclonal antibody.

10. The composition of claim 1, wherein said composition is in the form of a pharmaceutical composition.

11. The composition of claim 6, wherein said composition is in the form of a pharmaceutical composition.

12. A method of making a humanized monoclonal antibody which is capable of binding specifically with a PF4/heparin complex, wherein said antibody preferentially binds with said PF4/heparin complex relative to the binding of said antibody with either PF4 or heparin alone, said method comprising

a) obtaining a monoclonal antibody which is capable of binding specifically with a PF4/heparin complex, wherein said antibody preferentially binds with said PF4/heparin complex relative to the binding of said antibody with either PF4 or heparin alone;

b) humanizing said antibody in a), whereby a humanized monoclonal antibody is made.

13. The method of claim 12, wherein said monoclonal antibody in a) comprises a heavy chain polypeptide having an amino acid sequence which shares at least about 80% homology with SEQ ID NO:1 and a light chain polypeptide having an amino acid sequence which shares at least about 80% homology with SEQ ID NO:2.

14. The method of claim 12, wherein said monoclonal antibody in a) is a murine monoclonal antibody (KKO) which comprises the heavy chain polypeptide of SEQ ID NO:1 and the light chain polypeptide of SEQ ID NO:2.

15. A method of diagnosing HIT/HITT in a mammal, said method comprising

a) assessing the level of a polyclonal antibody in a sample of a bodily fluid or tissue obtained from said mammal, wherein said polyclonal antibody binds specifically with a PF4/heparin complex and preferentially binds with said PF4/heparin complex relative to the binding of said polyclonal antibody with either PF4 or heparin alone; and

b) comparing the level of said polyclonal antibody in said sample with the level of a monoclonal antibody which is specific for the PF4/heparin complex in a positive control sample for HIT/HITT, wherein said monoclonal antibody preferentially binds with said PF4/heparin complex relative to the binding of said monoclonal antibody with either PF4 or heparin alone;

c) determining from a) and b) whether the level of said polyclonal antibody in said sample is statistically similar to the level of said monoclonal antibody in said positive control sample, wherein when the level of said polyclonal antibody is statistically similar to the level of said monoclonal antibody in said positive control sample, then HIT/HITT is diagnosed in said mammal.

16. The method of claim 15, wherein said mammal is a human.

17. The method of claim 15, wherein said monoclonal antibody is a murine monoclonal antibody comprising a heavy chain polypeptide of SEQ ID NO:1 and a light chain polypeptide of SEQ ID NO:2.

18. The method of claim 15, wherein said level of said polyclonal antibody and said level of said monoclonal antibody are each assessed using an assay independently selected from the group consisting of an ELISA assay, a Western blotting assay, a serotonin release assay, a platelet aggregation assay, a lumi-aggregometry assay and a flow cytometry assay.

19. A method of assessing the level of a polyclonal antibody in a bodily fluid or tissue sample obtained from a mammal, wherein said polyclonal antibody binds specifically with a PF4/heparin complex and preferentially binds with said PF4/heparin complex relative to the binding of said polyclonal antibody with either PF4 or heparin alone, said method comprising

a) assessing the level of said polyclonal antibody in said bodily fluid or tissue sample obtained from said mammal;

b) comparing the level of said polyclonal antibody in said sample with the level of a monoclonal antibody which is specific for said PF4/heparin complex in a reference standard which comprises said monoclonal antibody, wherein said monoclonal antibody preferentially binds with said PF4/heparin complex relative to the binding of said monoclonal antibody with either PF4 or heparin alone;

c) determining from a) and b) the level of said polyclonal antibody in said sample, whereby the level of said polyclonal antibody in said sample is assessed.

20. A method of identifying a functional element of an antibody, wherein said functional element participates in the pathogenesis of HIT/HITT in a mammal, said method comprising

a) preparing one or more deletion or substitution mutants of a monoclonal antibody which bind specifically with a PF4/heparin complex and which preferentially bind with said PF4/heparin complex relative to the binding of either PF4 or heparin alone, wherein said one or more deletion or substitution mutants lack a portion of the amino acid sequence of the Fab region of said monoclonal antibody;

b) assessing the ability of each of said deletion or substitution mutants to bind specifically with a PF4/heparin complex and to preferentially bind with said PF4/heparin complex relative to the binding of said deletion or substitution mutant with either PF4 or heparin alone;

c) identifying, from b) one or more of said deletion or substitution mutants which does not preferentially bind with said PF4/heparin complex relative to the binding of said deletion or substitution mutant with either PF4 or heparin alone ; and

d) determining from c) and a) the corresponding deleted portion of the amino acid sequence of said monoclonal antibody which participates in said preferential binding with said PF4/heparin complex, whereby a functional element of said monoclonal antibody which participates in the pathogenesis of HIT/HITT is identified.

21. The method of claim 20, wherein said monoclonal antibody comprises a heavy chain polypeptide having an amino acid sequence which shares at least about 80%

homology with SEQ ID NO:1 and a light chain polypeptide having an amino acid sequence which shares at least about 80% homology with SEQ ID NO:2.

22. A method of treating HIT/HITT in a mammal, said method comprising

a) administering to said mammal a composition comprising a monoclonal antibody or a functional element thereof which binds specifically with a PF4/heparin complex and which preferentially binds with said PF4/heparin complex relative to the binding of said monoclonal antibody with either PF4 or heparin alone, wherein said monoclonal antibody or said functional element thereof is present in said composition in an amount effective to competitively inhibit the specific binding of a polyclonal antibody in the mammal to said PF4/heparin complex;

b) inhibiting the specific binding of said polyclonal antibody in said mammal with said PF4/heparin complex, thereby treating HIT/HITT in the mammal.

23. The method of claim 22, wherein said mammal is a human.

24. The method of claim 22, wherein said monoclonal antibody comprises a heavy chain polypeptide having an amino acid sequence which shares at least about 80% homology with SEQ ID NO:1 and a light chain polypeptide having an amino acid sequence which shares at least about 80% homology with SEQ ID NO:2.

25. The method of claim 22, wherein said monoclonal antibody is a humanized antibody.

26. The method of claim 22, wherein said monoclonal antibody is a murine monoclonal antibody comprising a heavy chain polypeptide having SEQ ID NO:1 and a light chain polypeptide having SEQ ID NO:2.

27. A method of identifying a compound which is a modulator of the specific binding of an antibody to a PF4/heparin complex, said method comprising,

a) contacting said compound with said antibody and said PF4/heparin complex; and

b) assessing the effect of said compound upon the specific binding of said antibody to said PF4/heparin complex, wherein a higher or lower level of specific binding of said antibody

to said PF4/heparin complex in the presence of said compound compared with the level of specific binding of said antibody to said PF4/heparin complex in the absence of said compound is an indication that said compound is a modulator of the specific binding of an antibody to a PF4/heparin complex.

28. The method of claim 27, wherein said antibody is a monoclonal antibody.

29. The method of claim 27, wherein said antibody is a polyclonal antibody.

30. The method of claim 27, wherein said antibody is a murine monoclonal antibody comprising a heavy chain polypeptide which shares at least about 80% homology with SEQ ID NO:1 and a light chain polypeptide which shares at least about 80% homology with SEQ ID NO:2.

31. The method of claim 27, wherein said antibody is a murine monoclonal antibody comprising a heavy chain polypeptide which is SEQ ID NO:1 and a light chain polypeptide which is SEQ ID NO:2.

32. A kit for diagnosing HIT/HITT in a mammal, said kit comprising

a) a positive control solution comprising a monoclonal antibody or a functional element thereof which binds specifically with a PF4/heparin complex, wherein said monoclonal antibody or said functional element thereof preferentially binds with said PF4/heparin complex relative to the binding of said monoclonal antibody or said functional element thereof with either PF4 or heparin alone; and

b) an instructional material describing the use of said positive control solution for diagnosing HIT/HITT in a mammal.

33. The kit of claim 32, wherein said monoclonal antibody comprises a heavy chain polypeptide having an amino acid sequence which shares at least about 80% homology with SEQ ID NO:1 and a light chain polypeptide having an amino acid sequence which shares at least about 80% homology with SEQ ID NO:2.

34. The kit of claim 32, wherein said monoclonal antibody is a murine monoclonal antibody (KKO) comprising a heavy chain polypeptide of SEQ ID NO:1 and a light chain polypeptide of SEQ ID NO:2.

35. The kit of claim 32, wherein said monoclonal antibody is a humanized antibody.

36. A kit for use in treating a mammal afflicted with HIT/HITT, said kit comprising

a) a composition comprising a monoclonal antibody or a functional element thereof which binds specifically with a PF4/heparin complex, wherein said monoclonal antibody or said functional element thereof preferentially binds with said PF4/heparin complex relative to the binding of said monoclonal antibody or said functional element thereof with either PF4 or heparin alone, wherein said monoclonal antibody or said functional element thereof is present in said composition in an amount effective to competitively inhibit the specific binding of a polyclonal antibody in said mammal to said PF4/heparin complex; and

b) an instructional material describing the use of said composition for the treatment of HIT/HITT in said mammal.

37. The kit of claim 36, wherein said monoclonal antibody is a humanized antibody.

38. The kit of claim 36, wherein said monoclonal antibody comprises a heavy chain polypeptide having an amino acid sequence which shares at least about 80% homology with SEQ ID NO:1 and a light chain polypeptide having an amino acid sequence which shares at least about 80% homology with SEQ ID NO:2.

39. The kit of claim 36, wherein said monoclonal antibody is a murine monoclonal antibody (KKO) comprising a heavy chain polypeptide of SEQ ID NO:1 and a light chain polypeptide of SEQ ID NO:2.